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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,561	03/11/2005	Ihor E. Kopka	21204P	7320

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/527,561	KOPKA ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,11,13-17,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11,17 and 24* is/are rejected.

7)☒ Claim(s) *13-16 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included addition of new claim 25, cancellation of claims 3 and 12 and amendment to claims 1, 2-9, 11 and 24, filed on 3/30/2006, is made of record. Claims 1, 2, 4-9, 11, 13-17, 24 and 25 are now pending.

In view of applicants' response, 112 second paragraph rejection made in the previous office action has been obviated. Applicants have overcome some of the 102/103 rejections made in the previous office action. However, the following rejections made in the previous office action are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 16 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating obesity and or eating disorder, does not reasonably provide enablement for treating all diseases and disorders mediated by cannabinoid (CB-1), receptor including preventing obesity. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.

The instant claim 11 is drawn to treating a cannabinoid receptor mediated disease by inhibiting the activity of cannabinoid receptor in general or CB-1 receptor in specific. The scope of the claim includes several specific diseases besides obesity and

eating disorder but there is no corresponding enabling disclosure. The instant compounds are disclosed to have cannabinoid receptor inhibitory activity and it is recited that the instant compounds are therefore useful in treating all diseases stated in the claim11 for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cannabinoid receptor inhibitor that would be useful for all sorts of diseases and disorders , including psychosis, memory deficit, cognitive disorders, migraine, neuropathy, neuroinflammatory disorders, cerebral vascular accident, and head trauma anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders, constipation and chronic intestinal pseudo-obstruction, cirrhosis of the liver, asthma, obesity and other eating disorder. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as Alzheimer's disease Parkinson's disease, cancers , autoimmune diseases are very difficult to treat and despite the fact that there are many drugs, which can be used for "inflammatory condition".

The scope of the claim 16 includes not only treating but also "preventing obesity " which is not adequately enabled solely based on the activity of the compounds as inhibitors of cannabinoid-1 receptor activity provided in the specification.

"To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the

instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the thousand of diseases embraced by the terms a disease or disorder.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Petrocellis et al., British Journal of Pharmacology, 141, 765-774, 2004, especially the concluding paragraph.. See also Black, Curr. Opin.. Investig. Drugs 5(4): 389-394, 2004 (PubMed Abstract provided)

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require cannabinoid receptor inhibitory activity.

2) The state of the prior art: Recent publications expressed that the cannabinoid receptor inhibition effects are unpredictable and are still exploratory. See references cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of cannabinoid receptor inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all diseases or disorders and cancers including those yet to be related to cannabinoid receptor activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action but limited to claim 11 and claim 16. Applicants' argument Applicants have amended the method of use claims to recite specific diseases and have asserted that each of the disease is supported by literature. However, upon careful analysis of these literature show not all

diseases embraced in claim 11 are supported. For example, applicants point to page 2 lines 10-13 but the study shows how to increase blood flow using CB1 receptor modulators. There are support documents for eating disorders , obesity. But there appears to no support for cognitive disorders, migraine, neuropathy, neuroinflammatory disorders, cerebral vascular accident, and head trauma anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders, constipation and chronic intestinal pseudo-obstruction, cirrhosis of the liver. Applicants are urged provide such documents for treating all these diseases to obviate this rejection.

As for preventing obesity, the passage applicants have pointed to mere defines a scale used establish what is to be regarded as obese. That is the scale means who are obese. This is not the same saying who will be obese. Prior art does not lend support for preventing obesity. Hence the rejection of claims 11 and 16 is proper and is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 4-8 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Agarwal et al., WO 2004/009560 for reasons of record. To repeat:

Agarwal et al. teaches several substituted pyrimidine compounds useful as cyclooxgenase inhibitors for treating pain and other diseases, which include instant compound generically claimed in the instant claims. See page 9, formula I and note the definition of A, R1, R2, R3, R4, R5 and R6. Note with a given A choice, when R5 and R6 are either aryl or heteroaryl, compounds taught by Agarwal et al. include instant compounds. See entire document, especially pages 13-17 for various substituted pyrimidine compounds. Particularly see page 16, species on line 9-11, 13, 14 and 18. See also examples 7 through 15, pages 33-37, wherein the starting material uracils are also claimed in the instant claims.

This rejection is same as made in the previous office action but now excludes cancelled claim 2. Applicants' traversal to overcome this rejection was not persuasive. Applicants have relied on the "oxo" group of the reference as feature not present in the instant claims. As noted above, instant claims read on the compounds of the reference when both R^1 and R^2 are OR^a and R^a is H, thus providing hydroxyl group at 2 and 4-position. This would tautmerize to the oxo group. Thus, instant claims include oxo groups as part of the definition of R^1 and R^2. Especially see examples 13 and 14 both of which meet the R^g requirement of instant claims.

Hence, this rejection is proper and is maintained.

Claims 1,2, 4-8 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Agarwal et al., WO 03/084935.

Agarwal et al. teaches several diaryl pyrimidine compounds useful as cyclooxgenase inhibitors for treating pain and other diseases, which include instant compound generically claimed in the instant claims. See page 9, formula I and note the definition of A, B, R1, R2, R3, R4, R5, R6, R7 and R8. Note with a given A and B choices, when R5 and R6 form a double bond, compounds taught by Agarwal et al. include instant compounds. See entire document, especially pages 14-15 for various substituted pyrimidine compounds which include several compounds claimed in the instant claims. See page 38-47, examples 5-20 for compounds made.

This rejection is same as made in the previous office action but now excludes cancelled claim 2. Applicants' traversal to overcome this rejection was not persuasive. Applicants have relied on the "oxo" group of the reference as feature not present in the instant claims. As noted above, instant claims read on the compounds of the reference when both R^1 and R^2 are OR^a and R^a is H, thus providing hydroxyl group at 2 and 4-position. This would tautmerize to the oxo group. Thus, instant claims include oxo groups as part of the definition of R^1 and R^2. Especially see examples 13 and 20 both of which meet the R^9 requirement of instant claims.

Hence, this rejection is proper and is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-9, 17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agarwal et al., WO 2004/009560 for reasons of record. To repeat:

Teachings of Agarwal et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Agarwal et al. teaches several substituted pyrimidine compounds useful as cyclooxgenase inhibitors for treating pain and other diseases, which include instant compound generically claimed in the instant claims.

Agarwal et al. differs from the instant claims in exemplifying only some of the compounds embraced in the genus of compound of formula I shown in page 9.

However, Agarwal et al. teaches equivalency of those compounds taught in pages 16, and 33-37 with those generically recited in pages 9-10.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Agarwal et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action but cancelled claims are excluded from this rejection. This rejection is maintained for reasons stated in the above 102 rejection. In summary, Agarwal et al., anticipates instant compounds and also teaches equivalency those compounds exemplified with those generically claimed.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Agarwal et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Hence, this rejection is maintained.

Claims 1-2, 4-9, 17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agarwal et al., WO 03/084935 for reasons of record.

Teachings of Agarwal et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Agarwal et al. teaches several substituted pyrimidine compounds useful as cyclooxgenase inhibitors for treating pain and other diseases, which include instant compound generically claimed in the instant claims.

Agarwal et al. differs from the instant claims in exemplifying only some of the compounds embraced in the genus of compound of formula I shown in page 9.

However, Agarwal et al. teaches equivalency of those compounds taught in page 38-47, examples 5-20, with those generically recited in pages 9-10.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Agarwal et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action but cancelled claims are excluded from this rejection. This rejection is maintained for reasons stated in the above 102 rejection. In summary, Agarwal et al., anticipates instant compounds and also teaches equivalency those compounds exemplified with those generically claimed.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Agarwal et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Hence, this rejection is maintained.

Allowable Subject Matter

Claims 13-16 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is (571) 272-0661.

The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

6/26/2006